Remarks

Reconsideration of this Application is respectfully requested.

Claims 13-16 and 18-30 are pending in the application, with claims 13 and 23 being the independent claims.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejection under 35 U.S.C. § 103

Claims 13-16 and 18-30 stand rejected under 35 U.S.C. § 103(a) as being obvious over WO 96/16048. (Office Action, page 2). Applicants respectfully traverse this rejection.

WO 96/16048 is published in the German language. It is believed that U.S. Patent No. 5,789,430 to Jautelat *et al.* ("Jautelat") is the English language equivalent to WO 96/16048. For simplicity, Applicants shall refer to Jautelat.

In reference to WO 96/16048, the Examiner stated:

WO 96/16048 discloses the combination of prothioconaozole with other fungicides, including tebuconazole, for treatment of fungal infections, including Erysiphe species, Puccinia species and Fusarium species, to widen the spectrum of action, to prevent build of resistance and that the activity of the mixture in many cases exhibits synergistic activity and that the formulations are prepared in a known manner, for example by mixing the active compounds with surfactants and extenders, and that application concentrations of the active compounds depend on the nature and occurrence of the microorganisms to be controlled and on the composition of the material to be protected and the optimum amount to be employed can be determined by a series of tests, including 250, 125 and 25 g/ha (see entire reference, especially, Page 40, Pg. 42, lines 11-15, Pg. 43, lines 15-30, Pgs. 44, 47, 56-67).

WO 96/16048 discloses that prothioconazole can be combined with other fungicides, including tebuconazole, and the combination can be synergistic. The difference between WO 96/16048 and the claimed invention is that WO 96/16048 does not expressly disclose the combination of prothioconazole with tebuconazole. However, the prior art amply suggests the same as WO 96/16048 discloses the combination of prothioconazole with other fungicides, including tebuconazole, and that the combinations can be synergistic. As such, it would have been well within the skill of and one of ordinary skill in the art would have been motivated to combine prothioconazole with tebuconazole with the expectation that the combination would be more effective than each alone.

(Office Action, pages 2-3). Applicants respectfully disagree.

A. A Prima Facie Case of Obviousness Has Not Been Established

a. Summary of Jautelat

Jautelat generally discloses triazolyl derivatives of formula (I) (encompassing prothioconazole), which have microbicidal actions and can be used to control undesirable microorganisms:

(Jautelat, Abstract.) Jautelat also specifically discloses 67 compounds including prothioconazole (*Id.* at col. 14, line 27, through col. 21, line 42, Table 1; col. 35, lines 10-20; and col. 38, line 32, through cols. 39 and 40, Table 2; prothioconazole is Preparation Example 1). Jautelat further states that:

When used in plant protection, the active compounds according to the invention can be used as such or, in their formulations, also as a mixture with known fungicides, bactericides, acaricides, nematicides or

insecticides, for example so as to widen the spectrum of action or to prevent the build up of resistance. In many cases, this results in synergistic effects, i.e. the activity of the mixture exceeds the activity of the individual components.

(Id. at col. 32, lines 24-31.) Jautelat then lists 163 fungicides, 13 bactericides, and 195 "insecticides/acaricides/nematicides" as "suitable components" for the mixture; one of the listed fungicides is tebuconazole. (Id. at col. 32, line 32, through col. 34, line 23.) However, Jautelat does not disclose any particular combinations, much less a combination of prothioconazole and tebuconazole. Thus, at most, Jautelat discloses prothioconazole, which can be combined with a laundry list of other active compounds.

b. The Person Of Ordinary Skill In The Art Would Have Had No Reason To Select Prothioconazole And Tebuconazole From A List Of Hundreds Of Combinations in Jautelat.

Applicants are aware of the flexible approach for establishing obviousness set out in KSR Int'l Co. v. Teleflex, Inc., 550 U.S. 398 (2007). However, as cautioned by Judge Rader in a post-KSR decision in In re Kubin, 561 F.3d 1351 (Fed. Cir. 2009), "where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness." (Id. at 1359). In rendering the rejection, the Examiner selected prothioconazole from Jautelat and then picked tebuconazole from a vast number of optional mixing partners disclosed therein, based on impermissible hindsight using the present specification as a blueprint. Furthermore, even if one would have picked and chosen presently claimed combination, one would not have the expectation other than a merely additive effect of the combination since there is no direct teaching by Jautelat, in which of the many cases which type of synergy neight be obtained. As such, Applicants contend that the Examiner's rejection is based on impermissible hindsight.

The Examiner cited In re Kerkhoven, In re Crockett and Ex Parte Quadranti to support the rejection. The Examiner stated:

It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art. *In re Kerkhoven*, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be prima facie obvious.). See also *In re Crockert*, 126 USPQ 186 (CCPA 1960) (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held prima facie obvious).

* * *

Contrary to the Applicant's arguments, In re Kerkhoven and In re Crockett are on point. Both prothicocanazole and tebuconazole are disclosed in the cited reference to be known fungicides and their combined use in the treatment of fungal infections on crops is suggested by the cited reference. Furthermore, the Applicant's evidence of synergy is not sufficient to overcome the prior art rejection as the cited reference discloses that the combinations can be synergistic. As such, synergy is not unexpected.

(Office Action, pages 3-5). Applicants respectfully disagree. Applicants submit that the facts in the present application are far removed from In re Kerkhoven, and thus its holding should not be broadly applied to the present invention for the following reasons. In re Kerkhoven dealt with the patentability of claims directed to a process of preparing a spray-dried detergent by mixing together spray-dried nonionic detergents and anionic detergents. In re Kerkhoven, 205 U.S.P.Q. 1069 (CCPA 1980). According to the United States Court of Customs and Patent Appeals ("CCPA"), the appealed claims "require no more than the mixing together of two conventional spray-dried detergents." Id. at 1072.

Applicants note that the appealed claims in *In re Kerkhoven* only require combining a spraydried nonionic detergent with a spray-dried anionic detergent, and do not require combining a specific nonionic detergent with a specific anionic detergent. Hence, the holding of *In re Kerkhoven* cannot be broadly applied to the present invention because, contrary to the facts in *In re Kerkhoven*, the present claims 13-16 and 18 require combining two specific fungicides, prothioconazole and tebuconazole, with specific mixing ratio ranges. In sum, because the facts in *In re Kerkhoven* are not analogous to that of the present invention, its holding should not be broadly applied to the present invention.

Applicants also submit that the facts in the present invention are removed from In re Crockett. In re Crockett dealt with the patentability of claims reciting, inter alia, methods treating gray iron prior to casting with a combination of calcium carbide and finely divided rare earth oxide or manganese dioxide, to produce an as-cast product containing uncombined carbon in nodular form. In re Crockett, 279 F.2d 274, 275 (CCPA 1960). The obviousness rejections of method and composition claims reciting the combination of calcium carbide and manganese dioxide were affirmed in view of prior art that directly suggested the specific method and composition, respectively. Id. at 276. However, an obviousness rejection of the method claim reciting calcium carbide and a rare earth oxide was reversed because the cited prior art did "not clearly suggest that cerium or cerium compounds would be similarly useful in cast iron." Id. at 277.

In contrast to the factual situation in *In re Crockett*, Jautelat provides no reason why a person of ordinary skill in the art would have selected tebuconazole among the other 163 fungicides, 13 bactericides, and 195 "insecticides/acaricides/nematicides" for mixture with prothioconazole.

Finally, Ex parte Quadranti, 25 U.S.P.Q.2d 1071 (Bd. Pat. App. & Inter. 1992), cited by the Examiner, does not stand for the proposition that all mixtures of herbicides are prima facie obvious. There are no per se rules of obviousness as each invention must be evaluated in view of the particular facts according to the paradigm set forth by the U.S. Supreme Court in Graham v. John Deere. The Quadranti decision turned in part on a lack of evidence that the Colby formula was considered valid by a significant number of ordinary skilled workers. Id. at 1072.

Contrary to the lack of evidence in Quadranti, Applicants provided with the Amendment and Reply dated September 8, 2010, overwhelming evidence that a broad consensus of authority accepts the Colby formula as a reliable measurement of synergy. Applicants cited in the First Supplemental Information Disclosure Statement a total of 24 articles describing the use of the Colby formula in calculating expected efficacies of herbicide combinations. For example, in Bauer et al., "Response of Selected Weed Species to Postemergence Imazethapyr and Bentazon," Weed Tech. 9:236-242 (1995), "Iffor the herbicide combinations, the expected weed control value was calculated following Colby's method (4)" (id. at page 237); in Blackshaw et al., "Herbicide Combinations for Postemergent Weed Control in Safflower (Carthamus tinctorius)," Weed Tech. 4: 97-104 (1990), "[p]lant responses to herbicide combinations were determined using Colby's method (9)" (id. at page 98); in Bradley et al., "Response of Sorghum (Sorghum bicolor) to Atrazine, Ammonium Sulfate, and Glyphosate," Weed Tech. 14: 15-18 (2000), "[e]xpected values for herbicide interactions were calculated using the Colby equation (Colby 1967)" (id. at page 16); Burke, et al., "CGA-362622 Antagonizes Annual Grass Control with Clethodim," Weed Tech. 16: 749-754 (2002), "[t]he expected response for herbicide mixtures and sequential treatments was calculated according to Colby (1967)" (id. at page 751); in Gillespie, G.R. & Nalewaja, J.D., "Wheat (Triticum aestivum) Response to Triallate Plus Chlorsulfuron," Weed Tech. 3:20-23 (1989), "[elquations previously described by Colby (3) were used to indicate synergistic or antagonistic interactions following the application of various triallate plus chlorsulfuron treatments" (id. at page 20); in Green et al., "Metribuzin and Chlorimuron Mixtures for Preemergence Broadleaf Weed Control in

Soybeans, Glycine max," Weed Tech. 2: 355-363 (1988), "[m]ixture observations were compared to the expected responses predicted by Colby's equation (6, 9)" (id. at page 356): in Harker, N.K., & O'Sullivan, P.A., "Synergistic Mixtures of Sethoxydim and Fluazifop on Annual Grass Weeds," Weed Tech. 5: 310-316 (1991), "Colby's method was used to predict 'Expected' plant responses to herbicide combinations" (id. at page 311); in Lanclos et al., "Glufosinate Tank-Mix Combinations in Glufosinate-Resistant Rice (Oryza sativa)," Weed Tech. 16: 659-663 (2002), "filhteractions between herbicide mixtures were calculated by the mathematical method described by Colby (1967)" (id. at page 660); in Norris et al., "Weed Control from Herbicide Combinations with Three Formulations of Glyphosate," Weed Tech. 15: 552-558 (2001), "[t]he method described by Colby (1967) was used to calculate the expected values of control from herbicide combinations" (id. at page 554); in Palmer et al., "Broadleaf Weed Control in Soybean (Glycine max) with CGA-277476 and Four Postemergence Herbicides," Weed Tech. 14: 617-623 (2000), "[t]he method described by Colby (1967) was used to calculate expected levels of control from herbicide tank mixtures" (id. at page 619); in Scott et al., "Spray Adjuvant, Formulation, and Environmental Effects of Synergism from Post-Applied Tank Mixtures of SAN 582H with Fluazifop-P. Imazethapyr, and Sethoxydim," Weed Tech. 12: 463-469 (1998), "[t]he method described by Colby (1967) was used to calculate interactions of herbicide tank mixtures" (id. at page 465); in Shaw, D.R. & Arnold, J.C., "Weed Control from Herbicide Combinations with Glyphosate," Weed Tech. 16: 1-6 (2002), "Colby's (1967) method was used to calculate synergistic, antagonistic, or additive responses of herbicide tank mixtures" (id. at page 2); in Zhang et al., "Fenoxaprop Interactions for Barnyardgrass (Echinochloa crus-galli) Control in Rice," Weed Tech. 19: 293-297 (2005), "[i]nteractions between fenoxaprop and other herbicides were calculated by the mathematical method described by Colby (1967)" (id. at page 294); and in Flint et al., "Analyzing Herbicide Interactions, A Statistical Treatment of Colby's Method," Weed Tech. 2: 304-309 (1988), the authors stated that "[t]he use of Colby's method is desirable because most researchers understand the concept and assumptions" (id. at page 307).

Thus, for at least these reasons, Applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness. Withdrawal of the rejection is respectfully requested.

B. Synergistic Effects Shown in the As-Filed Specification and Dahmen Declaration Rebut Any Case of Prima Facie Obviousness

As discussed above, the Examiner has not established a *prima facie* case of obviousness of the present claims. Moreover, the record clearly demonstrates that *prima facie* obviousness, even if it were established, is overcome by the synergistic, unexpected results obtained with the claimed combination. Synergistic effects have long been recognized as an indicator of non-obviousness.

The Examiner asserted the Colby formula is "not a reliable measurement of synergy," (Office Action, page 5), in view of Rummens, "An Improved Definition of Synergistic and Antagonistic Effects," Weed Science 23: 4-6 (1975). According to the Examiner, the "Colby equation can create an antagonism where none is present." id. Applicants note that Rummens' reference to the Colby formula is not the same as Applicants' formula (Specification, page 22-23), since Rummens uses the transformed version where "percent-of-control" values can be used instead of the percent of inhibition as in the present application (cf. the original document of Colby cited on page 22 of the specification). Applicants further note that Rummens concedes the Colby "technique" is a "standard method" of calculating synergism. (Rummens, page 4). As discussed above, there is substantial evidence that the Colby formula is a widely accepted method for calculating synergistic, antagonistic or additive effect of herbicide mixtures. Rummens was published in 1975. The 24 Weed Tech. articles cited in the accompanying Supplemental Information Disclosure Statement were published after 1975, and provide evidence that persons of

ordinary skill in the art accept the Colby formula. The earlier publication by Rummens is not evidence sufficient to overcome this overwhelming evidence.

With respect to the data in the specification, the Examiner asserted that:

the Specification does not appear to show trend in the data that would allow one of ordinary skill in the art to extend the probative value thereof. See In re Clemens, 622 F.2d 1029, 1036, 206 USPO 289, 296 (CCPA1980), Except for Example 1, none of the other examples provide efficacy data for the amounts used in the mixture applied in the same amount individually for both prothioconazole and tebuconazole. As such, it cannot be determined from those examples whether the amounts used in the mixture were synergistic. In Example 5 (treatment of Erysiphe infection on wheat), the efficacies of prothioconazole at 25, 12.5 and 6.25 g/ha were 75, 50 and 25%, respectively and the efficacy of tebuconazole at 25 g/ha was 88%. Since the maximum efficacy that a combination of said agents at the amounts indicated could not exceed %100, the data provided in fact provides evidence that the combination of prothioconazole and tebuconazole at the ratio of 1:1 to 1:3 is not synergistic. With respect to example 1 (pretreatment of cucumber prior to inoculation with Sphaerotheca), at an application rate of 2.5 g/ha for each agent, the actual efficacy for the mixture was 85% with the efficacies of the agents applied individually adding up to 71%. Since there is no indication as to the number of trials and/or number of plants treated, or statistical analysis of the values (the Examiner assumes that the values are averages), it does not appear that the value of 85% is significantly greater than 71%. As such, the data provided by the Applicant is not sufficient to show synergy at the ratio of 1:1 to 1:3 much less the entire range.

The data in the Specification, in addition to the above, shows that efficacy data can vary depending on a number of factors, including amount applied, fungi, treatment or pretreatment and/or habitat treated. For example, the efficacy at 25 g/ha of prothioconazole and tebuconazole varied from 75% and 88%, respectively in treatment of Erysiphe infection on wheat to 19% and 27%, respectively in treatment of Rhizoctonia solani infection on cotton seeds (See Example 5 and Example 11). As such, in view of the above, as the claims encompass treatment of any fungi and/or pre-treatment of any fungi's environment, even if the data was sufficient to show unexpected activity, the evidence is not commensurate in scope with the claimed invention.

(Office Action, pages 5-6). Applicants respectfully disagree. The data in the specification provides a showing of synergy over a substantial range, allowing the person of ordinary skill to ascertain a trend in the data. Applicants reproduce the data of Example in Table A below.

Table A: Data from Table 1 (pages 25-34) of the Specification as filed Sphaerotheca test (cucumber) / protective

Compound (Ratio)	Application	Efficacy in %	Calculated Efficacy using
	Rate in g/ha		the Colby Formula
Prothioconazole (I)	2.5	21	
Tebuconazole (III)	2.5	50	
(I) + (III) (1:1)	2.5 + 2.5	85	61

The data clearly shows synergism according to the Colby formula. In attacking the probative value of the data of Example 1, the Examiner stated that the addition of both individual efficacies was the proper comparison data point (71%) as opposed to the efficacy calculated according to the Colby formula. The Examiner has improperly supplied his own opinion regarding how to calculate synergy which is at odds with the practice of those of ordinary skill in the art, as discussed above.

Applicants reproduce that data of Example 5 in Table B below.

Table B: Data from Table 5 (pages 42-44) of the Specification as filed Ervsiphe test (wheat)/curative

Compound (Ratio)	Application Rate in g/ha	Efficacy in %
Prothioconazole (I)	25	75
	12.5	50
	6.25	25
Tebuconazole (III)	25	88
(I) + (III) (1:1)	12.5 + 12.5	100
(I) + (III) (1:3)	6.25 + 18.75	100
(I) + (III) (3:1)	18.75 + 6.25	100

Applicants note that much lower application rates of tebuconazole (12.5, 18.75 and 6.25 g/ha) were applied together with prothioconazole and compared to when tebuconazole was applied alone (25 g/ha). The Examiner has not acknowledged this lower application rate when evaluating the unexpected results. It would have been surprising and unexpected to the person of ordinary skill in the art that lowering the application rates of both components by from 50 to 75%, and combining the components at the lowered application rates would provide the much improved efficacy of the combinations (100%) compared to the efficacy of any single component tested alone at higher individual application rates.

Applicants reproduce the data of Example 6 in Table C below.

Table C: Data from Table 6 (page 48) of the Specification as filed Erysiphe test (wheat)/protective

Compound (Ratio)	Application Rate in g/ha	Efficacy in %
Prothioconazole (I)	6.25	57
Tebuconazole (III)	6.25	57
(I) + (III) (1:1)	3.125 + 3.125	79
(I) + (III) (1:3)	1.5625 + 4.6875	71
(I) + (III) (3:1)	4.6875 + 1.5625	71

Applicants note that much lower application rates of prothioconazole and tebuconazole were applied together compared to when applied individually. The Examiner has not acknowledged this lower application rate when evaluating the unexpected results. It would have been surprising and unexpected to the person of ordinary skill in the art that lowering the application rates of both components by from 25 to 75%, and combining the components at the lowered application rates would provide a much improved efficacy of the combinations compared to the efficacy of any single component tested alone at the higher individual application rates.

Applicants reproduce the data from Example 11 in Table D below.

Table D: Data from Table 11 (page 58) of the Specification as filed
Rhizoctonia solani test (cotton)/ seed treatment

Compound (Ratio)	Application Rate in g/ha	Efficacy in %
Prothioconazole (I)	25	19
Tebuconazole (III)	25	27
(I) + (III) (1:1)	12.5 + 12.5	40

Applicants note that much lower application rates of prothioconazole and tebuconazole were applied together compared to when applied individually. The Examiner has not acknowledged this lower application rate when evaluating the unexpected results. It would have been surprising and unexpected to the person of ordinary skill in the art that lowering the doses of both components by 50%, combining the components at the lowered doses, and testing the combination would provide a much improved efficacy of the combination compared to the efficacy of any single component tested alone at the higher individual dose.

In In re Kollman, the CCPA stated that "the unobviousness of a broader claimed range can, in certain instances, be proven by a narrower range of data. Often, one having ordinary skill in the art may be able to ascertain a trend in the exemplified data which would allow him to reasonably extend the probative value thereof." In re Kollman, 595 F.2d 48, 56 (CCPA 1979). In the present application, Applicants have demonstrated a synergistic effect of the claimed invention at different mixing ratios, against different fungi and on different crops/plants. A person of ordinary skill in the art would have been able to ascertain a trend in the exemplified data to reasonably extend such data to a broader claimed range as recited in claim 13. In addition, claims 14 and 16 are directed to a synergistically effective

composition comprising prothioconazole and tebuconazole, wherein the mixing ratio of prothioconazole to tebuconazole is 1:0.33 to 1:3 (claim 14); or is from 1:1 to 1:3 (claim 16), respectively. Claims 14 and 16 are much narrower in scope compared to Claim 13. In view of the evidence of unexpected synergistic effects presented in the specification, a person of ordinary skill in the art would have been able to ascertain a trend in the exemplified data of Tables 1, 5, 6, and 11 to reasonably extend such data to the claimed ranges as recited in claims 13, 14 and 16. Similarly, claims 18-22 are directed to methods for controlling fungi, cereal diseases and specifically the cereal diseases Erysiphe, Puccinia and Fusarium by using the composition according to claim 16. Applicants have demonstrated the unexpected synergistic effect obtained with the claimed composition against *Sphaerotheca fuliginea* (Specification as filed, Table 1, page 33), *Erysiphe graminis f.sp. hordei* (Id, Tables 5 and 6, pages 41-48), and *Rhizoctonia solani* (Id, Table 11, page 58).

Applicants furthermore present the Declaration of Peter Dahmen under 37 C.F.R. § 1.132, labeled Exhibit A, as further evidence of unexpected results of the present invention. This new data compares efficacy for the same amounts of prothioconazole and tebuconazole when applied individually and as a mixture, thus addressing the Examiner's concern on page 5, lines 10-12, of the Office Action.

In the Example labeled "Fusarium graminearum test (barley) / preventive," young barley plants were sprayed with a 1:3 preparation of prothioconazole and tebuconazole. After the spray coating had dried, the plants were injured using a sandblast and then sprayed with a conidia suspension of Fusarium graminearum. Five (5) days afterward the plants were evaluated. The tested 1:3 preparation of prothioconazole and tebuconazole provided a synergistic effect compared to when the single compounds were applied.

In the Example labeled "Leptosphaeria nodorum test (wheat) / preventive," young wheat plants were sprayed with a 3:1 preparation of prothioconazole and tebuconazole. After the spray coating had dried, the plants were sprayed with a spore suspension of Leptosphaeria nodorum. Eight (8) days afterward the plants were evaluated. The tested 3:1

preparation of prothioconazole and tebuconazole provided a synergistic effect compared to when the single compounds were applied.

In the Example labeled "Fusarium nivale (var. majus) test (wheat) / preventive," young wheat plants were sprayed with a 1:1 preparation of prothioconazole and tebuconazole. After the spray coating had dried, the plants were injured using a sandblast and sprayed with a conidia suspension of Fusarium nivale (var. majus). Five (5) days afterward the plants were evaluated. The tested 1:1 preparation of prothioconazole and tebuconazole provided a synergistic effect compared to the single compounds.

For the reasons set forth above, Applicants respectfully request that the Examiner reconsider the evidence of unexpected synergistic effects presented in the specification and that the rejection be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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